Depletion Rates of Injected and Ingested Ivermectin from Blood Serum of Penned White-Tailed Deer, *Odocoileus virginianus* (Zimmermann) (Artiodactyla: Cervidae)

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ABSTRACT Penned female and male white-tailed deer, *Odocoileus virginianus* (Zimmerman), were administered ivermectin both by direct subcutaneous injection and by ingestion of ivermectin-medicated whole kernel corn. Depletion rates of ivermectin were determined by biweekly and weekly assays of blood serum. No statistical differences were observed between mean peak ivermectin serum concentrations in deer (data of sexes combined) from injection and ingestion studies, and ivermectin concentrations decreased to below detectable within 21 d after injection and 14 d after ingestion.

KEY WORDS tick control, pharmacokinetics, acaricide, medicated bait

IN THE UNITED STATES, white-tailed deer, *Odocoileus virginianus* (Zimmermann), are the primary large wild animal hosts for parasitic stages of the lone star tick, *Amblyomma americanum* (L.) (Patrick and Hair 1978, Bloemer et al. 1986, 1988). This tick is the presumed primary vector for the agent causing human monocytic ehrlichiosis, *Ehrlichia chaffeensis* Anderson, Dawson, Jones, and Wilson (Lockhart et al. 1996). Deer are also the keystone host for adults of the blacklegged tick, *Ixodes scapularis* Say (Barbour and Fish 1993). This species transmits the agent causing Lyme disease, *Borrelia burgdorferi* Johnson, Schmid, Hyde, Steigerwalt, and Brenner, in the eastern United States. Pound et al. (1996) used a systemically active acaricide, ivermectin, to control lone star ticks feeding on white-tailed deer. They demonstrated the importance of white-tailed deer as major hosts for maintenance of lone star tick populations, but more importantly, they determined that employing acaricides to control parasitic ticks feeding on white-tailed deer also could significantly reduce populations of free-living ticks in the treatment area. The concept was further substantiated in field trials in which pesticide was applied topically to white-tailed deer that were attracted to and fed from the patented "4-poster" passive topical treatment device (Pound et al. 1994, 2000a, b).

Use of ivermectin in food animals in the United States requires a period of withdrawal before slaughter, milking, etc. of treated animals. The Food and Drug Administration (FDA) mandates clearance of the drug from animal products that could be consumed by humans, and ivermectin is currently not labeled for use in humans in the United States. It is unlikely that the ivermectin-medicated bait technology mentioned above would be approved for use in white-tailed deer to control the fall cohort of adult blacklegged ticks that feed during October, November, and December, a time that coincides with the white-tailed deer hunting season. However, a systemic acaricide such as ivermectin or another macrocyclic lactone perhaps might be used to control the spring feeding cohort of adult blacklegged ticks after close of the hunting season. This would allow a withdrawal period sufficient for depletion of the drug from animal tissues before the beginning of the fall hunting season. Similar spring-summer treatments for lone star ticks would impact both adult and immature ticks feeding on the deer. In both scenarios, the length of the withdrawal period would be inversely related to the rate of depletion of the drug from selected tissues of the deer, i.e., the greater the rate of depletion, the shorter the imposed withdrawal time. To assist in establishing a withdrawal period for ivermectin in deer, the current study determined the rates of depletion for both injected and ingested ivermectin from blood serum of penned white-tailed deer.

Materials and Methods

White-tailed deer used in the ivermectin injection study were from stocks maintained at the Texas Department of Parks and Wildlife, Kerr Wildlife Management Area, Hunt, TX. Handling, housing, feeding, treatment, etc. were under direct supervision of management area personnel. Six bucks (males) and six

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does (females) were gathered and housed with three does each in two large pens, two bucks each in two large pens, and two bucks held individually in two smaller pens. Deer were provided water and specially formulated 19% protein deer pellets (Bode Feed and Supply, Harper, TX) ad libitum.

On day 0, deer were weighed, restrained in a drop-chute, and injected subcutaneously with ivermectin (Ivomec Injectable; Merial, Rahway, NJ) at dosages of 200 μg/kg body weight. Previous studies determined that the peak concentration of ivermectin in serum of cattle would occur ≈3 d after injection (Fink and Porras 1989). To assay the approximate peak and weekly serum concentrations thereafter, duplicate 10-ml vials of blood were obtained from each deer on days 3, 7, 14, and 21 after injection. Blood samples were assayed for serum ivermectin concentration using techniques developed by Oehler and Miller (1989) by extracting the ivermectin through a reverse-phase C_{18} cartridge, further purifying with a silica-packed cartridge, and quantifying by liquid chromatography with detection at 245 nm.

After determining that serum ivermectin concentrations had dropped below the minimum detection level of 2 ppb, these same six does and six bucks were used in a second trial. This experiment was designed to assay the rate of ivermectin depletion from blood serum of deer that were allowed to self-dose by ingesting whole kernel corn coated with ivermectin. When provided with pellet food and corn ad libitum, deer consumed ≈0.45 kg of corn per 45 kg of body weight per day (J.M.P. and J.A.M., unpublished data). Corn was formulated with the target dose of 10 mg ivermectin/0.45 kg corn, anticipating that each deer would consume ≈0.45 kg treated corn per 45 kg of body weight per day. Corn was prepared using an electric cement mixer to mix 22.7 kg (50 lb) with 100 ml Ivomec Pour-on (Merial) (Pound et al. 1996).

Deer were allowed to feed ad libitum on a diet of 19% protein deer pellets, ivermectin-coated whole kernel corn, and water for 16 d. Blood serum samples and analyses confirmed that medicated corn was being consumed at approximately the anticipated rate, and the decision was made to terminate treatment (remove treated corn) 4 d later on the day 20 of treatment. The 19% protein pellets and water continued to be supplied ad libitum. The first blood serum samples were taken 4 d before cessation of treatment (day −4), at cessation of treatment (day 0), and on days 3, 7, and 14 after cessation of treatment.

Descriptive statistics and repeated measures analysis of variance (ANOVA) were calculated using the SAS System for Windows (SAS Institute, Cary, NC) and SigmaStat for Windows (SPSS, Chicago, IL).

In conducting the research described here, we adhered to protocol approved by the U.S. Department of Agriculture, Agricultural Research Service Animal Welfare Committee. The protocol is on file at the USDA–ARS, Knipling-Bushland U.S. Livestock Insects Research Laboratory, Kerrville, TX.

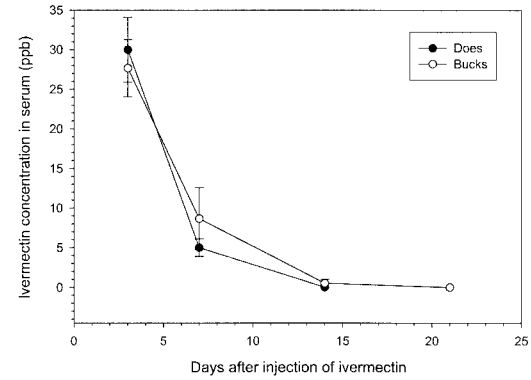

Fig. 1. Mean concentrations (ppb) of ivermectin in blood serum of doe and buck white-tailed deer on days 3 (presumed peak after injection), 7, 14, and 21 after injection.

Results

Depletion of serum ivermectin concentrations in white-tailed deer that received standard, single subcutaneous injections of ivermectin is shown in Fig. 1. Serum ivermectin concentrations on day 3 after injection were near the anticipated peak dosage of 30 ppb, with statistically similar mean concentrations of 30.0 and 27.7 ppb ($t = -0.67$; df = 1,30; $P = 0.5058$) being present in does (range, 14–40 ppb) and bucks (range, 20–44 ppb), respectively. By 14 d after injection, ivermectin concentrations declined to <2 ppb in 11 of the 12 deer, and concentrations were below detectable in all deer by 21 d. The single deer that had detectable serum ivermectin on day 14 after injection was a buck that had declined to 3 ppb from a high of 26 ppb observed on day 3 after injection.

Depletion of serum concentrations after ingestion of ivermectin-medicated whole kernel corn is shown in Fig. 2. Because the same buck that had detectable serum ivermectin on day 14 after treatment in the injection study above also developed a serious antler/foot infection and ate poorly, data for this animal were

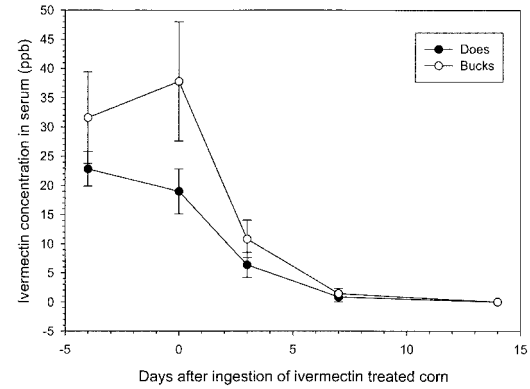

Fig. 2. Mean concentrations (ppb) of ivermectin in blood serum of doe and buck white-tailed deer on days −4, 0 (day of cessation of treatment), 3, 7, and 14 after ingestion of ivermectin-medicated whole kernel corn.

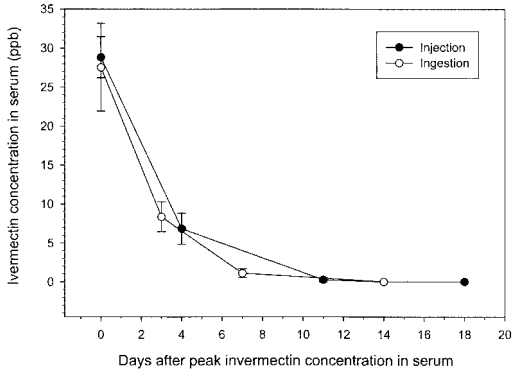

Fig. 3. Mean concentrations (ppb) of ivermectin in blood serum of combined doe and buck white-tailed deer administered ivermectin by injection and ingestion on the day of peak concentration and intervals thereafter.

omitted from analysis in the ingestion study. Positive serum samples from the 11 remaining deer 4 d before cessation of treatment (day −4) confirmed ivermectin ingestion. Serum ivermectin concentrations on day −4 did not differ by sex and were 22.8 (does: range, 11–31 ppb) and 31.6 ppb (bucks: range, 13–53 ppb) ($t = 1.50$; df = 1,36; $P = 0.1417$). The combined mean for the 11 deer was 26.8 ppb. When feeding of medicated corn was discontinued (day 0), mean concentrations in does (range, 14–38 ppb) had decreased to 19.0 ppb, whereas in bucks (range, 14–65 ppb), the mean had increased to 37.8 ppb. Although serum concentrations of does versus bucks were significantly different on day 0 ($t = 3.22$; df = 1,36; $P = 0.0027$), the combined mean concentration for the 11 deer on day 0 of 27.5 ppb was not significantly different from the 26.8 ppb ($t = -0.30$; df = 1,40; $P = 0.7663$) observed previously on day −4. After cessation of treatment on day 0, the mean serum concentrations of the 11 deer declined to 8.4, 1.1, and <2 ppb on days 3, 7, and 14, respectively.

Depletion of serum ivermectin for both injection and ingestion studies with peak ivermectin concentrations adjusted to day 0 are shown in Fig. 3 (sexes pooled). The overall difference between injection and ingestion groups was not significant ($F = 0.01$; df = 1,21; $P = 0.9237$). In addition, no statistical differences in mean serum concentrations were observed between injection day 0 and ingestion day 0 ($t = -0.36$; df = 1,73 ; $P = 0.7178$), between injection day 4 and ingestion day 3 ($t = 0.43$; df = 1,73; $P = 0.6676$), between injection day 11 and ingestion day 7, or between injection day 18 and ingestion day 14 ($t = 0.00$; df = 1,73; $P = 1.0000$).

Discussion

Pound et al. (1996) demonstrated ivermectin-medicated whole kernel corn controlled free-living populations of lone star ticks when fed daily to white-tailed deer confined in large pastures. Serum ivermectin concentrations in deer also were monitored for 2 yr and averaged 22 and 28 ppb. These results are consistent with both injection and ingestion data from the current study, and both studies demonstrate that free-choice ingestion of medicated corn is a reasonable method of administering desired doses of ivermectin to deer. Essentially 100% control of lone star ticks would result from serum ivermectin concentrations of 5–8 ppb (Nolan et al. 1985, Miller et al. 1989). Consequently, the three above examples of ivermectin administration to deer would provide good control of lone star ticks and probably many other parasites, even at the lowest observed concentration of 14 ppb.

Ivermectin serum concentrations declined rapidly in deer after either subcutaneous injection or ingestion of ivermectin-medicated whole kernel corn. Within 21 d after treatment, ivermectin concentrations were below the minimally detectable concentration of 2 ppb in all deer tested. The single deer with measurable ivermectin after 14 d was likely to be physiologically compromised because of a bacterial infection. To minimize stress on the deer, the decision was made not to sample blood between days 7 and 14. Had additional samples been taken, depletion of ivermectin to <2 ppb may have been documented somewhat earlier than day 14 after treatment. In addition, the rate of decline of ivermectin in the serum did not seem highly related to the initial concentration in the serum. Although initial serum concentration varied from 14 or 65 ppb, serum concentrations were below detectable levels in all deer at 21 d after treatment.

Although a statistical difference was observed between serum ivermectin concentrations in does and bucks in the ingestion phase of this study using penned deer, it is likely that this would not hold true at all times of the year in pastured or free-roaming deer, and it should not reduce efficacy against ticks. For example, Pound et al. (1996) observed only 3 ppb of ivermectin in serum in a pastured doe that had given birth to twin fawns 1–2 wk before being sampled and that the ivermectin concentration in this deer increased to 17 ppb 21 d later as she began to revisit the feeder along with her twin fawns.

In conclusion, ivermectin treatment of pastured white-tailed deer is an efficient, efficacious, and environmentally friendly method of reducing free-living populations of lone star ticks (Pound et al. 1996). It also may be useful in free-roaming deer in reducing free-living populations of other tick species for which the white-tailed deer is an important host. However, ivermectin currently is not approved for use in humans in the United States. It is unlikely that ivermectin would be labeled for use in deer until residue studies on a variety of tissues is completed, and a mandated withdrawal time before consumption of the treated deer by humans is established. This study demonstrates that even relatively high concentrations of ivermectin in blood serum of white-tailed deer decline to negligible levels in <21 d.

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